



Cost-Effectiveness of Tuberculosis Screening and Observed Preventive Therapy for Active Drug Injectors at a Syringe-Exchange Program

David C. Perlman, Marc N. Gourevitch, Chau Trinh,
Nadim Salomon, Leslie Horn, and Don C. Des Jarlais

ABSTRACT *This study examined whether costs associated with tuberculosis (TB) screening and directly observed preventive therapy (DOPT) among drug injectors attending a syringe exchange are justified by cases and costs of active TB cases prevented and examined the impact of monetary incentives to promote adherence on cost-effectiveness. We examined program costs and projected savings using observed adherence and prevalence rates and literature estimates of isoniazid (INH) preventive therapy efficacy, expected INH hepatotoxicity rates, and TB treatment costs; we conducted sensitivity analyses for a range of INH effectiveness, chest X-ray (CXR) referral adherence, and different strategies regarding anergy among persons affected with human immunodeficiency virus (HIV). For 1,000 patients offered screening, incorporating real observed program adherence rates, the program would avert \$179,934 in TB treatment costs, for a net savings of \$123,081. Assuming a modest risk of TB among HIV-infected anergic persons, all strategies with regard to anergy were cost saving, and the strategy of not screening for anergy and not providing DOPT to HIV-infected anergic persons resulted in the greatest cost savings. If an incentive of \$25 per person increased CXR adherence from the observed 31% to 50% or 100%, over a 5-year follow-up the net cost savings would increase to \$170,054 and \$414,856, respectively. In this model, TB screening and DOPT at a syringe exchange is a cost-effective intervention and is cost-saving compared to costs of treating active TB cases that would have occurred in the absence of the intervention. This model is useful in evaluating the cost impact of planned program refinements, which can then be tested. Monetary incentives for those referred for screening CXRs would be justified on a cost basis if they had even a modest beneficial impact on adherence.*

INTRODUCTION

Drug users have a high prevalence of *Mycobacterium tuberculosis* (MTb) infection and are at high risk for active tuberculosis (TB).^{1,2} Drug users are also at risk for human immunodeficiency virus (HIV) infection, which markedly increases the rates of reactivation of latent tuberculous infection.³ Isoniazid (INH) preventive therapy substantially reduces the risk of TB in both HIV-uninfected and HIV-positive individuals infected with MTb.⁴⁻¹⁰ The cost-effectiveness of self-administered TB preventive therapy, in general and among HIV-infected persons, has been demon-

Drs. Perlman, Salomon, and Des Jarlais, Ms. Horn, and Ms. Trinh are with Beth Israel Medical Center, New York City; Dr. Gourevitch is with Montefiore Medical Center, Bronx, New York.

Correspondence and reprints: David C. Perlman, MD, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY 10003. (E-mail: dperlman@bethisraelny.org)

strated.^{11–13} Hence, detection of TB infection and delivery of preventive therapy to drug users are important public health interventions.

However, TB screening and preventive therapy are multistep interventions, and the completion of TB screening and adherence to preventive therapy remain problematic in many settings and for many populations, including, but not limited to, drug users.^{2,14–16} The completion rates for INH preventive therapy range from 20% to 69%.^{17,18} Directly observed preventive therapy (DOPT), a valuable strategy in improving adherence and completion of therapy rates for persons with active TB, has also been suggested as a means of improving adherence to preventive therapy.^{17–22}

Drug treatment programs have been demonstrated to be valuable sites for both conducting TB screening (such screening is mandated in many settings) and delivering INH preventive therapy.^{2,19,23,24} Gourevitch et al.²⁵ found a program of DOPT at a methadone maintenance treatment program to be cost effective. However, an estimated 80%–90% of drug users are not in drug treatment at any given time.²⁶ Efficient means of delivering TB preventive therapy to active drug users not in treatment are therefore needed.

Syringe-exchange programs (SEPs) have the potential to deliver health interventions such as TB screening to this high-risk population. TB screening conducted on site at a SEP is acceptable to syringe-exchange participants.^{27,28} With a program model that includes a \$15 incentive, 94% of those accepting TB screening returned 48–72 hours later to have the tuberculin skin tests interpreted.^{27,28}

However, adherence of tuberculin-positive syringe-exchange participants to referral to off-site facilities for screening chest X-rays (CXRs) to exclude active TB prior to initiating preventive therapy has been limited (31%).²⁹ Incomplete adherence to this step of TB screening limits the ability to identify appropriate candidates for preventive therapy. Nonetheless, among those identified as eligible for TB preventive therapy, adherence has been good.²⁹

We examined the cost-effectiveness of conducting TB screening and DOPT for active drug injectors on site at a syringe exchange in an area of high HIV and TB prevalence compared to costs of treating cases of active TB that would have occurred in the absence of the intervention. We also examined the potential impact of the addition of monetary incentives to improve adherence to referral for screening CXRs on program cost-effectiveness.

METHODS

Overview

The hypothesis being tested was that costs incurred by a program of TB screening and DOPT at a SEP are lower than costs of treating cases of active TB that would have occurred in the absence of the intervention. The observed prevalence rates of MTb and HIV infection in the study population and observed program rates of voluntary acceptance of TB screening (95%), of returning for skin test interpretation (94%), and of adherence to referral for screening chest radiographs (31%) were used in the analysis.²⁷ Program costs included those of staff, supplies, rent, overhead, liver function tests, CXRs, INH, and monetary incentives for skin testing. To estimate cost-effectiveness, we used a modification of a model that examined the cost-effectiveness of DOPT with daily INH at a methadone maintenance treatment program in New York City.²⁵

We modified the original model to reflect direct costs and overhead at the SEP during the study period (1995–1996), the prevalence of MTb and HIV infection among SEP participants, and use of a twice-weekly preventive therapy regimen; to incorporate observed rates of adherence to each step of TB screening; and to examine the impact of monetary incentives on adherence rates and examine different strategies with respect to anergy. Throughout the text, the terms *cost saving* and *costs prevented* refer to comparison with costs of treating active TB cases that would have occurred without the program model under study.

We used published data to project the incidence of TB expected in the absence of preventive therapy, and projected the number of TB cases that would be expected to be averted by INH preventive therapy across a range of INH effectiveness.^{4–10,17,18,25,30,31} We then weighed the costs incurred by conducting the intervention (screening, excluding active disease with chest radiographs, providing DOPT, and monitoring for and managing hepatotoxicity) in a hypothetical 1,000 patients against the costs of managing the excess cases of TB that would have occurred in the absence of the intervention. We calculated the cost of screening and DOPT per TB case averted and the net savings associated with this intervention.

We also examined the potential impact of the addition of a monetary incentive designed to improve adherence to referral for screening CXRs for tuberculin-positive (and HIV-infected anergic) subjects for a range of adherence outcomes and again calculated the per case costs and net savings. Analyses were performed from a societal perspective^{32–34} and were designed to examine the cost-effectiveness of performing TB screening and DOPT for active drug injectors in an area of high HIV and TB prevalence. The study was approved by the Institutional Review Board of Beth Israel Medical Center, and informed consent was obtained from all participants.

Setting

The Lower East Side Needle Exchange Program (LESNEP) is one of several legally sanctioned syringe-exchange programs operating in New York City. It is a storefront facility located in the Lower East Side of Manhattan, an ethnically diverse inner-city area with a high prevalence of TB. The exchange has over 8,000 registered participants, it is open 6 days each week, and there are no chest radiograph or other medical facilities located on site.

Screening

Tuberculosis screening was offered to all exchange participants during syringe-exchange sessions as previously described.^{27–29} At first contact, participants were offered tuberculin and anergy skin testing, underwent a staff-administered interview, and were offered HIV counseling and testing. Accepting participants were asked to return 48–72 hours later, at which time they would receive \$15 (\$10 cash and \$5 transportation tokens).

Purified Protein Derivative Skin Testing Study participants were tested with 0.1 mL (5 TU) of tuberculin purified protein derivative (PPD) (Connaught Laboratories, Swiftwater, PA) placed intradermally on the volar aspect of the left forearm. To test for cutaneous anergy, 0.1 mL of mumps (Connaught Laboratories, Swiftwater, PA) and *Candida* antigens (Berkeley Biological, Berkeley, CA) were placed intradermally on the volar aspect of the right arm. The transverse diameters of induration for both PPD and anergy tests were measured with a millimeter ruler

at 48–72 hours. Interpretation was done by specifically trained health educators according to standard guidelines.³⁰ A positive PPD tuberculin test was defined as an induration of more than 10 mm in known HIV-negative persons and more than 5-mm induration in all others. Anergy was defined as less than 2 mm induration on all three skin tests.

Assessment of Patients for Preventive

Therapy Eligibility

Patients with a positive PPD (or with HIV infection and anergy) were evaluated for clinical TB. Patients underwent a focused clinical examination by a physician's assistant and were referred off site for free screening CXRs. Patients were provided with transportation tokens (\$5 cash equivalent) to facilitate access to the nearby radiology facility (15 blocks from the syringe exchange).

On-site DOPT with twice weekly INH was offered when active TB was excluded. When suspicious radiographic findings resulted in a confirmed or presumptive TB diagnosis, participants were referred elsewhere for directly observed TB therapy.

Directly Observed Preventive Therapy Protocol

Patients for DOPT were scheduled for twice weekly visits to receive INH 900 mg and pyridoxine 50 mg. Patients could be dosed on any two nonconsecutive days of the week (Monday through Saturday) during any time that the syringe exchange was open (10–11 AM until 8–11 PM on various days). An enabler (four transportation tokens, cash equivalent value \$6) was provided weekly for transportation to and from DOPT visits. Estimates are based on twice weekly dosing for a period of 26 weeks (i.e., 52 doses over 6 months). Clinically, DOPT was continued for up to 9 months in HIV-infected patients.

Monitoring for Isoniazid Toxicity

Patients were briefly questioned about potential adverse effects at dosing visits. Liver function tests were monitored monthly as the prevalence of viral hepatitis is high among injecting drug users, approximately half the cohort is over 35 years of age, alcohol abuse is prevalent in the study population, and the risk of hepatotoxicity may be increased in black and Hispanic women.^{18,30} DOPT patients were monitored monthly by physician assistants, who performed the venipunctures. Results were reviewed by supervising physicians, and if liver function tests were significantly elevated compared with prior determinations, patients underwent clinical evaluation for possible INH-related hepatotoxicity. INH was discontinued if toxicity was suspected.

Estimated costs of monthly monitoring included program costs for physician assistant time (10 minutes); venipuncture supply and laboratory testing; physician review time (3 minutes); and associated overhead costs. Estimates of costs associated with managing INH hepatotoxicity were based on data in previously published studies.^{31,35}

Modeling Estimates for Incidence and Costs of Tuberculosis

The assumptions in the model and the methods used to estimate TB incidence and costs and benefits associated with DOPT were based on an earlier model described in detail elsewhere.²⁵ Frequencies, costs, and event rates were entered into and ana-

lyzed in a relational database (Paradox, Version 5, Borland, Scotts Valley, CA). In modeling TB disease incidence, we determined the number of tuberculosis cases that would have arisen in the absence of DOPT over a 5-year period, incorporating the following assumptions²⁵:

1. The prevalence of HIV is based on actual data from the SEP population (to ascribe TB hazard rates to all subjects for the model, the proportion not clinically tested for HIV was assumed to be HIV infected at the same proportion as the tested population).
2. Mortality rates were derived from the literature.^{3,36-39}
3. Hazard rates for developing active TB among HIV-seronegative and HIV-seropositive persons were estimated from the literature^{3-10,39-41} and were held constant each year during the 5-year period.^{36,40}
4. High risk of tuberculosis disease among HIV-infected recent PPD converters was assumed.^{3-10,39,40}
5. There were no cases of TB developing during INH administration.^{4-6,25}
6. Active TB cases were all due to drug-susceptible isolates of MTb.^{4-6,25}

Costs were derived using the following assumptions:

1. The cost of treating a case of TB was considered to be the cost of a single hospitalization for an HIV-infected or HIV-uninfected person with TB in New York City, as appropriate.^{25,42}
2. The rate of health care inflation in the hospital sector would not exceed the conventional discount rate of 3% annually, and thus no discounting methods were employed in our analysis.^{25,42}
3. Additional costs of detecting, preventing, or treating TB infection or disease resulting from "secondary" cases among contacts of those developing active TB despite receiving DOPT were excluded both for simplicity in the model and to bias the model against finding the program cost effective or cost saving.²⁵ In addition, we included the costs of providing incentives to participants for CXR examinations.

To address issues of uncertainty in the model,^{25,32-34} we conducted sensitivity analyses for varying degrees of INH effectiveness and CXR referral adherence and as a function of the role of anergy in TB incidence. Because of uncertainty about the validity and importance of cutaneous anergy with respect to TB risk among HIV-infected persons^{39-41,43-46} and the uncertain role of preventive therapy in that setting,^{9,41,47} we examined in our model three scenarios that varied the effect of anergy on TB risk. One scenario ("no anergy") ignored anergy altogether by excluding costs of screening for anergy and excluding consideration of any possible excess risk of active TB among HIV-infected anergic persons. The second scenario included testing for anergy and assumed that HIV-infected anergic individuals have a moderately increased risk of developing TB, but that DOPT was not provided to them. The third scenario ascribed to HIV-infected anergic individuals a moderate risk of TB and included the provision of DOPT. For the second and third scenarios, we assumed anergy was associated with a relative hazard rate of TB incidence of 1.44 among HIV-positive anergic persons.⁴⁷ For the third scenario, we postulated that receipt of a full course of INH was associated with a 50% reduction in risk of

developing TB among HIV-positive anergic individuals; this was based on the risk ratios observed in preventive therapy trials for HIV-infected anergic subjects.^{9,41}

To examine the impact of varying CXR referral adherence on program cost-effectiveness, we examined the effect of varying degrees of adherence to CXR referral (30% to 100%) in response to monetary incentives.

RESULTS

The demographic characteristics of the first 974 syringe-exchange participants agreeing to TB screening are depicted in Table 1. Of those reporting previous reac-

TABLE 1. Demographic and skin test characteristics of study sample, N = 974 (%)

	N	(%)
Gender		
Male	648	(67)
Female	325	(33)
Age		
Median, years	33	N/A
<20 years	50	(5)
20–29 years	240	(25)
30–39 years	383	(40)
40–49 years	246	(25)
50–59 years	41	(4)
>60 years	5	(1)
Race/ethnicity		
Hispanic	270	(28)
Black	180	(19)
White	457	(47)
Other/unknown	59	(6)
Country of origin		
US born	847	(88)
Foreign born	115	(12)
Drug treatment history		
Ever in drug treatment	677	(72)
Never in drug treatment	269	(28)
Drug use in the past 6 months		
Any heroin	671	(65)
Any cocaine	565	(58)
HIV status		
HIV+	179	(18)
HIV–	642	(66)
Unknown	151	(16)
Previously told of PPD+ or TB PPD results	128	(13)
PPD positive	219	(23)
Anergic	102	(10)
PPD negative	653	(67)

N/A, not applicable; PPD, purified protein derivative.

*Column percentage may not total 100 due to rounding.

tive TB skin tests, 58% reported no prior or only incomplete courses of TB preventive therapy and were considered eligible for DOPT once active TB was excluded; 42% had previously completed courses and were deemed ineligible for preventive therapy. Overall, 17.5% of the subjects needed screening CXRs to exclude active TB and determine eligibility for preventive therapy (Fig.).

Table 2 depicts the costs associated with TB screening and with determining the eligibility for TB preventive therapy among a hypothetical 1,000 syringe-exchange participants. Costs include those for supplies, staff time and effort, incentives, and screening CXRs when indicated (using the New York State Medicaid reimbursement for postero-anterior and lateral CXRs), the costs of providing a cash equivalent of \$5 for transportation to the off-site radiology facility, and costs for physician review of the CXRs. Overhead costs included disposal of infectious waste and prorated costs of rental of the syringe-exchange storefront space.

Cumulative costs were calculated utilizing the actual rates of adherence to each of the steps of TB screening (Table 2; Fig.). For example, since 95% of the actual syringe-exchange participants approached for screening agreed to participate, 5% of the hypothetical 1,000 persons modeled (or 50 persons) were assumed to require only 5 minutes of effort by the program health educator, but did not contribute to skin testing or CXR screening costs. These participants were eliminated from the pool of subjects eligible for preventive therapy, but remained in the pool of subjects at risk for TB in the modeling of TB incidence. Similarly, since adherence to returning for skin test interpretation was 94% in the syringe-exchange cohort, 6% of subjects were assumed to contribute to costs associated with placing skin tests, but not to subsequent costs of interpreting skin tests, screening for TB disease, or preventive therapy eligibility. They also were excluded from the pool of persons who could benefit from prophylaxis, but were included in the pool of subjects at risk for incident TB. Further, since it is common practice in TB screening programs not to repeat skin tests on subjects reporting prior positive tests or prior TB, such subjects were not considered to contribute to skin testing costs, but were considered eligible for screening for preventive therapy eligibility if they reported not having completed prior TB preventive therapy.

Table 3 depicts the costs of providing INH preventive therapy, including costs

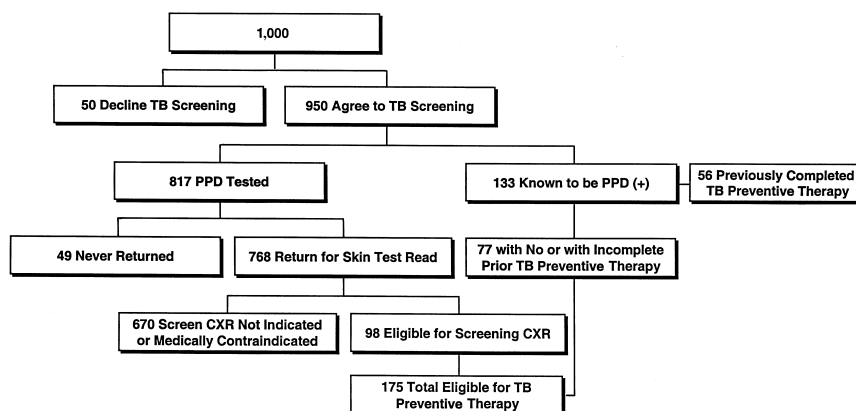


FIGURE. Outcomes of TB screening at syringe exchange for hypothetical 1,000 patients using actual program routes.

TABLE 2. Costs associated with screening for tuberculosis infection and disease and determining eligibility for chemoprophylaxis

Screening	Group	Item	Unit cost	Persons requiring	Total cost per item
TB infection	Approached, declined participation	Health educator, 5-minute visit	\$1.94	50	\$97.17
	History of prior positive PPD	Health educator, 5-minute visit	\$1.94	133	\$258.46
	Underwent PPD testing	PPD (1 5TU dose) and syringe	\$0.39	817	\$318.63
		Anergy Panel*†	\$4.60	817	\$3,758.20
		Health educator, 10-minute placement	\$3.89	817	\$3,178.13
		Health educator, 5-minute reading	\$1.94	768	\$1,492.48
		Physician, 1-minute assessment	\$1.21	768	\$927.36
		Subtotal			\$10,144.90
TB disease		Chest X-ray and associated costs‡	\$102.00	175	\$17,850.16
Eligibility for chemoprophylaxis		Baseline LFTs and associated costs§	\$38.55	175	\$6,745.40

PPD, purified protein derivative; TU, tuberculin units; LFTs, liver function tests.

*HIV-seropositive persons only.

†For scenario 1 (no anergy testing), the cost of the anergy panels and their administration is zero, reducing the subtotal costs to \$6,289.70.

‡Associated costs include subway tokens, review of results, and, for a fraction, escort to and from the test.

§Associated costs include phlebotomy and physician review.

of monitoring for INH-related hepatotoxicity, to the 17.5% of the cohort potentially eligible for TB preventive therapy (including HIV-positive anergic subjects), assuming all 100% had screening CXRs that excluded active tuberculosis.

Modeling Tuberculosis Incidence

Table 4 depicts the literature-derived estimated annual hazards of developing TB used in modeling the number of TB cases expected to develop in the absence of preventive therapy. Of tuberculin reactors, 10% were classified as recent converters (within the prior 2 years) and the remainder as chronic reactors (converted more than 2 years ago).

Using the costs depicted in Tables 2 and 3 and the estimates of annual TB hazard for the different HIV/PPD status subgroups (Table 4), we modeled the number of incident TB cases expected to develop in the presence or absence of INH preventive therapy and the projected associated costs of hospitalization for incident TB cases (Table 5).⁴⁷

TABLE 3. Costs of isoniazid chemoprophylaxis under direct observation and of associated clinical monitoring

	INH/B6-related costs,* \$		Monthly clinical monitoring costs, \$			No. of patients		Total costs, \$
	INH/B6	Direct observation by nurse (3 minutes)	Monthly LFTs*	Monthly PA monitoring visit (10 minutes)	Monthly MD monitoring visit (3 minutes)	Accepting		
						Eligible	INH/B6	
HIV–	33.80	60.63	224.66	43.47	21.74	41	41	15,756.30
HIV+ PPD+ and HIV+ anergic‡	67.60	121.26	449.32	86.94	43.47	45	45	34,586.55
HIV status unknown, PPD+	67.60	121.26	449.32	86.94	43.47	89	89	68,404.51
Total						175	175	118,747.36
Total cost/person								686.56

B6, vitamin B6 (pyridoxine); INH, isoniazid; LFTs, liver function tests; PPD, purified protein derivative.

*Costs are given per patient for 6- and 12-month courses of chemoprophylaxis for HIV– and HIV+ persons, respectively. Costs of \$0.14 per each 300-mg dose INH (ie., \$0.42 for 900 mg) and \$0.23 per dose of B6 each for two weekly doses for 26 weeks and of \$38.55 for each automated liver panel were used.

†Assuming that 100% of eligible persons actually undertake isoniazid chemoprophylaxis.

‡For scenario 1 (exclusion of the prevalence of anergy) and scenario 2 (HIV+ anergic individuals receiving no DOPT), number of patients eligible was 36.

TABLE 4. Skin test and HIV serologic status estimation of annual hazard of developing active tuberculosis*

Category	Year 1	Year 2	Year 3	Year 4	Year 5
HIV- PPD+					
New	0.02	0.01	0.005	0.005	0.005
Old	0.005	0.005	0.005	0.005	0.005
HIV+ PPD+					
New	0.2	0.1	0.09	0.08	0.07
Old	0.07	0.07	0.07	0.07	0.07
HIV+ anergic, unknown history	0.014	0.014	0.014	0.014	0.014

"New" denotes recent (within last 2 years) tuberculin test conversion; "old" denotes chronic (>2 years) history of reactive tuberculin test; PPD, purified protein derivative.

*Hazard estimates drawn from the literature.

Cost-Effectiveness as a Function of Isoniazid Effectiveness

Table 6 presents net cost savings at 3 and 5 years of follow-up for INH efficacy rates of 65% and 90%, reflecting the range in the published literature.^{3-10,17,38-41,47}

This analysis assumed that the HIV seroprevalence among subjects with unknown HIV status was 20%, reflecting that in the cohort of known serostatus, and that HIV-infected anergic persons had a moderate risk for TB and were offered DOPT; and the analysis incorporates the observed 31% adherence to CXR referral. The average savings accrued for each 10% increase in INH efficacy rate was \$96,251.

Cost-Effectiveness as a Function of Chest X-ray Referral

Adherence and Incentive Costs

Incomplete adherence to screening CXRs reduces the pool of subjects eligible for DOPT and increases the pool of subjects who remain at risk for incident TB. We examined the potential impact on overall cost-effectiveness of providing a \$25 monetary incentive for adherence to referral for screening CXRs. For an INH effective-

TABLE 5. Expected numbers of tuberculosis cases and associated hospital costs after 5 years of follow-up of 507 persons, by HIV serologic and skin test status and degree of isoniazid effectiveness*

INH effectiveness	HIV seronegative†				HIV seropositive†		Total	
	PPD positive		PPD positive		Anergic			
	Cases	Costs	Cases	Costs	Cases	Costs	Cases	Costs
No INH	3	\$78,668	14	\$537,989	1	\$38,428	18	\$655,084
40%	2	\$52,445	9	\$345,850	0	\$0	11	\$398,295
65%	1	\$26,223	5	\$192,139	0	\$0	6	\$218,361
90%	0	\$0	2	\$76,856	0	\$0	2	\$76,856

INH, isoniazid; PPD, purified protein derivative.

*Includes anergic individuals at risk for tuberculosis and who are offered DOPT.

†Assumes that 80% of HIV-unknown patients are HIV seronegative and 20% are seropositive.

TABLE 6. Modeling impact of isoniazid (INH) effectiveness and monetary incentives on chest X-ray adherence rates*

	Baseline model: actual CXR completion rate of 31% with no monetary incentive	Increase CXR adherence rate to 50% with \$25 cash incentive	Increase CXR adherence rate to 100% with \$25 cash incentive
Total TB cases prevented			
3-year follow-up			
INH .65	3	4	7
INH .90	3	5	11
5-year follow-up			
INH .65	3	5	12
INH .90	4	7	16
Total TB costs prevented			
3-year follow-up			
INH .65	\$103,078	\$141,506	\$256,789
INH .90	\$141,506	\$179,934	\$398,295
5-year follow-up			
INH .65	\$103,078	\$179,934	\$436,723
INH .90	\$179,934	\$256,789	\$578,229
Cost of program per case of TB averted			
3-year follow-up			
INH .65	\$18,951	\$21,684	\$23,339
INH .90	\$14,213	\$17,347	\$14,852
5-year follow-up			
INH .65	\$18,951	\$17,347	\$13,614
INH .90	\$14,213	\$12,391	\$10,211
Net savings			
3-year follow-up			
INH .65	\$46,226	\$54,770	\$93,416
INH .90	\$84,654	\$93,199	\$234,922
5-year follow-up			
INH .65	\$46,226	\$93,199	\$273,350
INH .90	\$123,081	\$170,054	\$414,856

*Using Anergy Model that includes anergic subjects and provides them with preventive therapy.

ness of 90%, if the incentive increased CXR referral adherence from 31% to 50% or 100%, cost savings at 5-year follow-up would increase from \$123,081 to \$170,053 and \$414,856, respectively (Table 6).

Cost-Effectiveness as a Function of the Role of Anergy in Tuberculosis Incidence

We examined impact of three anergy scenarios on the costs and net savings of the TB screening at the SEP (Table 7). The no anergy scenario (neither screening nor providing DOPT for anergic HIV-infected persons) removed 9 individuals from the original group of 175 subjects eligible for CXRs and preventive therapy (Fig.). Assuming a TB relative hazard rate for HIV-infected anergic subjects of 1.44 yielded a low number of TB cases, equivalent to the number in the no anergy sce-

TABLE 7. Modeling impacts of various anergy scenarios*

	No anergy, \$	Screen for anergy, moderate TB risk, no DOPT, \$	Screen for anergy, moderate TB risk, provide DOPT, \$
Screening costs	13,560	17,319	17,739
DOPT costs	8,499	8,499	9,160
Monitoring costs	36,088	26,088	28,117
Hepatotoxicity costs	1,837	1,837	1,837
Total costs	49,984	53,742	56,852
Total TB costs prevented			
3-year follow-up			
INH .65	103,078	103,078	103,078
INH .90	141,506	141,506	141,506
5-year follow-up			
INH .65	103,078	103,078	103,078
INH .90	179,934	179,934	179,934
Cost of program per case of TB averted			
3-year follow-up			
INH .65	16,661	17,914	18,951
INH .90	12,496	13,435	14,213
5-year follow-up			
INH .65	16,661	17,914	18,951
INH .90	9,997	10,748	14,213
Net savings			
3-year follow-up			
INH .65	53,094	49,336	46,226
INH .90	91,522	87,764	84,654
5-year follow-up			
INH .65	53,094	49,336	46,226
INH .90	129,950	126,192	123,081

DOPT, directly observed preventive therapy; INH, isoniazid.

*Using baseline Model of 31% Chest X-ray Adherence Rates with No Incentives.

nario. Hence, the total TB costs prevented for all three scenarios were the same across varying INH effectiveness rates and years of follow-up. Over a 5-year follow-up period, for INH efficacy rates of 0.65 and 0.90 the total costs prevented were \$103,078 and \$179,934, respectively.

The program costs per TB case averted were the greatest for the scenario that screened for anergy and provided anergic subjects with DOPT. Hence, the net savings at 3- and 5-year follow-up were greatest for the no anergy scenario compared with those that included anergy screening with or without the provision of DOPT.

DISCUSSION

Among drug users, TB is a serious health issue. Drug users have an increased prevalence of latent tuberculous infection and are at risk of active TB and of nonadherence to TB screening and therapy.^{1,2,24,48,49} Injection drug users are also at high risk

for HIV infection, and HIV infection is the most potent risk factor in promoting the reactivation of *M. tuberculosis* infection.^{3,18,39,50} TB in HIV-infected drug users has contributed significantly to the rise of TB in several developed countries.⁵¹ The spread of both HIV and injection drug use practices into regions in which TB has long been prevalent makes issues of TB in drug users relevant to developing countries as well.^{2,50,51}

Services for TB have been incorporated successfully into drug treatment programs.^{19,23,47,52} However, as most drug users are not in drug treatment at any given time, additional approaches to deliver such services are needed. Syringe-exchange programs are designed primarily to reduce HIV transmission. There are at least 101 syringe-exchange programs in the US⁵³ and many more throughout the world. Some provide a range of services designed to reduce the risk of other complications of ongoing injection drug use, including acute medical care on site, influenza and pneumococcal vaccination, and referrals to drug abuse treatment and to mental health and social services providers.^{27-29,54-56}

Of US syringe-exchange programs, 20% reported providing some TB screening services, and 10% provided directly observed therapy for TB.⁵³ Nonetheless, while drug treatment programs do provide TB skin testing, most do not provide on-site TB DOPT, and most syringe exchanges provide neither screening nor preventive therapy for TB. An important reason for the absence of these services is that neither drug abuse treatment nor syringe-exchange programs are funded to provide them.

We demonstrated that TB screening and DOPT at a syringe exchange in an area of high HIV and TB prevalence can also be a cost-effective intervention over a wide range of INH efficacy rates. The cost-effectiveness of the intervention was demonstrated by incorporating actual rates of adherence to different steps of the intervention. Cost-effectiveness analyses have often suffered from considering primarily the intrinsic efficacy of an intervention rather than its effectiveness in actual practice.^{11,32-34} The degree to which participants drop out from treatment can be more influential in determining the cost-effectiveness of TB treatments than the intrinsic efficacy of a regimen.¹¹

Operational impediments to TB screening and preventive therapy and limitations in the adherence to the different steps of TB screening are common to TB control programs throughout the world.^{14,15,57} In our setting, the major limiting step was that of referral for off-site CXRs. This diminished the potential of the TB screening to identify candidates for preventive therapy and thus decreased, but did not eliminate, the clinical value and cost-effectiveness of the TB screening and DOPT.

Monetary incentives have been found to be highly effective in promoting adherence to voluntary DOPT, in facilitating acceptance of and adherence to TB skin testing at SEPs, and in improving return rates for PPD interpretation.^{2,15,16,27} Monetary incentives may therefore have the potential to increase rates of CXR referral adherence.

We found that the use of monetary incentives for those referred for screening CXRs would be justified on a cost basis if it had even a modest beneficial impact on adherence. To our knowledge, the impact of monetary incentives on TB program cost-effectiveness has not previously been evaluated. Monetary incentives do pose significant program costs. Consequently, acceptance of incentives as a routine part of an ongoing clinical or public health program would require that the incentive effectively promote improved adherence, and that the benefits derived from such improved adherence offset the costs of the incentive program. These data demon-

strate that cost models may be useful in evaluating the financial impact of planned program refinements, such as incentives, which can then be tested.

Conflicting data about the validity and importance of anergy with respect to TB risk among HIV-infected persons^{3,39–41} and the uncertain role of preventive therapy in that setting^{9,41,47} led CDC to revise its guidelines to suggest that testing for anergy among HIV-infected persons need not be conducted routinely as a part of tuberculin screening.⁴⁶ Nonetheless, anergic HIV-infected individuals, particularly injecting drug users, may be at heightened risk of developing active TB compared to nonanergic persons,^{39,40,47,58,59} and although two trials of preventive therapy for HIV-infected anergic subjects did not identify a statistically significant TB risk reduction, the risk ratios associated with INH therapy were approximately 0.5 for both.^{9,41} Further, Sawert et al. found that INH preventive therapy for anergic HIV-infected persons may be justifiable on a cost basis in populations with a high prevalence of tuberculous infection.¹³

We therefore modeled three scenarios that varied the approach to anergy in the screening and DOPT program and used a conservative estimate of relative risk for TB (1.44) among anergic subjects.⁴⁷ We found that the greatest costs and least savings were associated with the strategy of testing for and providing DOPT to HIV-infected anergic persons, suggesting that this approach may not be justified on a cost basis if the relative hazard of incident TB in HIV-positive anergic persons is as low as 1.44 and the prevalence of anergy is also low. However, while the greatest savings were seen in the no anergy scenario, and the ability of the analysis to discriminate between models was limited by the modest number of anergic individuals in the study population, all the models yielded cost savings.

We found the program to be cost saving over the range of INH effectiveness reported in the literature. Because the benefit derived by INH preventive therapy is proportional to the number of doses taken, this analysis also effectively represents, for any given intrinsic degree of INH activity, the effect of varying degrees of adherence to INH preventive therapy on cost-effectiveness.^{4–6,18,60} Hence, these data suggest that the intervention may remain cost saving even with variable adherence.

The advent of highly active antiretroviral therapy can reduce the risk of tuberculosis among HIV-infected drug users through immune restoration.⁶¹ However, the extent to which the potential benefits of costly, complicated, multiple-drug antiretroviral regimens will actually affect TB risk among populations of active drug injectors remains uncertain. Further, Gourevitch et al. found that DOPT at a methadone maintenance treatment program remained cost effective even if they modeled a 50% lower TB hazard among HIV-infected, PPD-positive drug users.²⁵

To bias our model against finding our program cost effective, we made several conservative assumptions. We incorporated costs for routine monthly liver function test monitoring for those on INH, which may not always be indicated, because of the high background prevalence of risk factors for hepatotoxicity in populations of drug users. We did not incorporate the costs of treatment for drug-resistant TB, the costs of multiple hospitalizations for a single TB case, outpatient costs of TB care, or the costs of preventing or treating secondary MTb infections or secondary cases of active TB. However, these also would have increased resultant cost savings. We relied on an INH-based regimen rather than a 2-month preventive therapy regimen of rifampin (or rifabutin)–pyrazinamide as the applicability of this regimen to persons actively abusing opiates may be limited by the drug-drug interaction between opiates and rifamycins.^{2,50,62,63}

The cost model was based on HIV and tuberculin reactivity prevalence rates

and TB treatment and DOPT costs at this study site and on available TB hospitalization and hepatotoxicity management cost data, which are ever changing; the cost savings accrued will vary based on the balance of these and other factors in different settings and at different times. The frequency and length of hospitalizations for TB, and hence costs, may depend on the extent of associated homelessness and lack of health insurance in a population.⁶⁴ However, there are over 1 million injection drug users in the US,² with a prevalence of MTb infection greater than that in the general population,^{1,2} representing an important reservoir of MTb infection, and if our results could be generalized to the national level, cost savings could be substantial.

We conclude that TB screening and DOPT at SEPs is an efficient and cost-effective strategy for reducing TB among active drug users, generating protective benefits for the individual and diminishing future TB treatment costs. In our analyses, the cost savings identified accrue to society as a whole, rather than to the individuals being screened or to the syringe-exchange program itself.³²⁻³⁴ On a cost basis, there would be little incentive for a syringe-exchange program to fund TB screening and on-site preventive therapy as the potential savings accrued would be realized not by the syringe-exchange program, but by the health care delivery systems that would otherwise have borne the costs of TB treatment. The generalizability of the model would therefore depend on the funding and staffing available to conduct such programs. However, important public health benefits might accrue if funding for TB screening and preventive therapy interventions at SEPs and for creating linkages between clinical/public health providers and SEPs were allocated, for example, by or through agencies and programs (e.g., health departments, Medicaid, or other insurers) that would otherwise have borne the costs of TB treatment.

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